REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

As set forth in the Office Action Summary, claims 1-3 and 5-23 are pending. Claims 1, 5, 6, 10, 11, 12, and 13 are amended herein. New claims 24-25 are added. Basis for the amendments and new claims may be found throughout the specification and claims as-filed, especially at page 15, lines 29-31, page 16, line 19, and claim 8 as-filed, as well as page 16, lines 6-9 (new claim 24) and page 16, lines 9-12 (new claim 25).

Claims 8-9 are canceled herein without prejudice or disclaimer thereto. Applicants reserve the right to file at least one continuation application directed to any subject matter canceled herein.

Claim Objections

Claim 9 is objected to, as the Office asserts that the phrase "said poxviral particle is an IMV" is redundant to base claim 1. Claim 9 is deleted herein, and thus this objection is moot.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1-3, 5, 6, 8-15 and 18 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite.

Claim 1 stands rejected for the recitation of "heterologous ligand moiety", as the Office states that the term "heterologous" indicates that the ligand has different components, but that the nature of these components remains undefined.

First, Applicants refer to page 7, lines 8-9, of the specification. Here the term "heterologous" is defined such that the ligand moiety is not found at the surface of a wild-type poxviral particle, *i.e.*, heterologous with respect to the components of the poxvirus particle. In the interest of expediting prosecution, the term "heterologous" has been removed from the claims, such that only "ligand moiety" is recited.

Claim 1 stand further rejected, for the recitation of "capable of binding an anti-ligand molecule", as the Office asserts that it is unclear whether the heterologous ligand moiety binds to the anti-ligand with specificity or whether any ligand capable of binding an anti-ligand applies.

Applicants refer to page 7, lines 10-13, which states that the interaction between the ligand moiety present at the surface of the poxviral particle and its corresponding anti-ligand molecule present at the surface of the target cell is specific. To clarify this point, claim 1 is amended herein to recite "wherein said specificity is conferred by the binding of at least one ligand moiety which is localized at the surface of said poxviral particle, to an anti-ligand molecule localized at the surface of said target cells".

Claim 5 stands rejected for the recitation of "capable of". Claim 5 is amended herein to replace "is capable of binding" with "binds". Claim 5 stands further rejected for the recitation of "heterologous ligand moiety is capable of binding ... a cellular protein differentially or overexpressed" on tumor cells. The Office questions how a

cellular protein that is differentially or overexpressed may serve as an anti-ligand for targeting tumor cells, when normal cells would also express the cellular protein.

It is well known in the art that a number of cellular proteins are involved in the tumoral development. For example, Applicants refer to cellular antigens which express during the feto-embryonic period and regress at birth until disappearing. Antigens which are normally expressed at a very low level may become characteristic of a tumor when expressed as a high level (and whose structure or conformation is modified). The MUC-1 antigen is an illustrative example of overexpressed cellular protein associated with tumor development. The MUC-1 polypeptide is a highly glycosylated mucin which is normally found at the apical surface of mucin-secreting epithelial cells in many types of tissues. The function of the mucin is to lubricate and protect epithelial cells from the harsh environment of the lumen. The onset of cancer in organs including breast, prostate, lung, pancreas, ovaries, and uterus may be accompanied by an over expression of the MUC-1 antigen by tumor cells. The MUC-1 polypeptide overexpressed by tumor cells is less glycosylated than normal MUC-1 version, revealing new peptide epitope and carbohydrate moiety, such as those recognized by the murine monoclonal antibody SM3. For example, a ligand moiety which comprises an antibody or part thereof of the SM3 antibody would be able to bind tumor-associated MUC-1 epitopes resulting in the targeting of MUC-1 expressing tumor cells.

Thus, in light of what is know in the art in combination with the disclosure of the present specification, Applicants submit that the skilled artisan would understand what is meant by the phrase "heterologous ligand moiety is capable of binding ... a cellular protein differentially or overexpressed".

Claim 8 stands rejected for the recitation of "wherein said heterologous ligand moiety is a polypeptide and wherein it is part of a chimeric protein encoding said heterologous ligand moiety and poxviral polypeptide ...". Claim 8 is canceled herein, and thus this rejection is moot

Claim 11 stands rejected for the recitation of "wherein said heterologous ligand moiety comprises a signal peptide facilitating its insertion in the envelope of said poxviral particle". The Office argues that it is unclear whether "its" refers to the ligand moiety or just to the signal peptide. To clarify that the term "its" refers to the ligand moiety, claim 11 is amended herein to recite "that said ligand moiety further comprises a signal peptide facilitating the insertion of said ligand moiety in the envelope ...".

The Office further asserts that the type of peptides falling within the scope of claim 11 is unclear. In response, Applicants submit that the mechanism of cellular transport and the signal involved were well known in the art in common, well known books accessible to one skilled in the art, at the time the present application was filed. For example, it is well known that in eukaryotes, most secretory proteins and proteins which are transported to and/or through organelles are synthesized as precursor polypeptides containing N-terminal signal peptides which permit translocation to specific cellular destination. Then, these N-terminal signal peptides are cleaved during the translocation process.

Thus, Applicants submit that it would be understood what is meant by "wherein said heterologous ligand moiety comprises a signal peptide facilitating the insertion ..." and request that the rejection be withdrawn,

Claim 12 stands rejected for the recitation of "the signal peptide allows the translocation of said heterologous ligand moiety in the trans-Golgi network", as the Office states that the description of how the heterologous ligand moiety behaves in a cell does not describe the ligand's physical characteristics. In response, Applicants submit that the Golgi-targeting signal sequences are well known in the art. For example, as set forth on page 17 of the specification, these sequence can be isolated from any protein naturally present in the Golgi compartment.

Moreover, the specification cites a review article describing the signal peptides allowing translocation of polypeptide entities through the Golgi compartment (*e.g.*, Muesch et al., 1990) as well as two scientific publications that illustrate representative examples of Golgi-targeting signal peptides, *e.g.*, in the membrane proteins of the Golgi complex (*e.g.*, Machamer, 1993), and in the coronavirus E1 glycoprotein (*e.g.*, Machamer and Rose, 1987). Accordingly, Applicants respectfully request that the rejection of claim 12 be withdrawn.

Claim 13 stands rejected for the recitation of "wherein said signal peptide is derived from ... TGN51", as the Office asserts that the use of "derived from" is indefinite. In the interest of expediting prosecution, claim 13 is amended herein to remove the term "derived from" and to add the phrase "the signal peptide is the signal peptide of the human trans-Golgi network glycoprotein TGN51".

Claim 15 stands rejected for the recitation of "suicide gene", as the Office argues that the term lacks a clear meaning. However, Applicants submit that this term does have a clear meaning, as evidenced in references published prior to the filing of the present application. For example, Adachi et al. (2000, Human Gene Ther. 11:77) states on page 77, at the top of the second column, that "Prodrug/gene-

directed enzyme therapy (suicide gene therapy), a promising strategy, describes the transfer of suicide genes into tumor cells to render them sensitive to prodrugs that are relatively non-toxic to normal tissues. One of the most intensively studied suicide gene therapies, ganciclovir/herpes simplex thymidine kinase (HSV TK) gene therapy ... has already been tried for clinical patients with malignant brain tumors". Applicants also refer to Kianmanesh et al. (1997, Human Gene Ther. 8:1807) which is dedicated to suicide gene therapy.

Further, the specification does provide reference to suicide genes. Pages 20-21 of the present specification specifically discuss the suicide genes as used with the present invention, and defines them as encoding an expression product able to transform an inactive prodrug into a cytotoxic substance (*see* specifically page 20, lines 22-24).

In light of the above, Applicants respectfully request that the rejections pursuant to 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-3, 5, 6, 8-15 and 18 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly failing to enable the skilled artisan to practice the full scope of the claimed invention without undue experimentation. Specifically, the Office asserts that the specification provides no working example or another explanation as to how the skilled artisan may produce a heterologous targeting ligand that omits the signaling moiety of the p14 polypeptide.

In the interest of expediting prosecution and without acqueising in the rejection, the claims as amended herein now cover the insertion of the ligand moiety in the p14 poxviral polypeptide.

Thus, the present claims, as depending on independent claim 1, are directed to a poxviral particle having a targeted infection specificity to target cells, wherein the specificity is conferred by the binding of at least one ligand moiety. The ligand moiety is localized at the surface of the poxviral particle to an anti-ligand molecule localized at the surface of the target cells. The poxviral particle is an intracellular mature virus (IMV). The ligand moiety is a polypeptide fused to a poxviral polypeptide localized at the surface of the IMV poxviral particle such that a chimeric polypeptide is produced. The poxviral polypeptide localized at the surface of the IMV poxviral particle is the expression product of the A27L gene.

In light of the above, Applicants submit that undue experimentation would not be required in order to produce ligand of the present claims. Applicants request that this rejection be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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